Primary cutaneous CD8+ small- to medium-sized Lymphoproliferative disorder in extrafacial sites: Clinicopathologic features and concept on their classification

Kempf, Werner ; Kazakov, Dmitry V ; Cozzio, Antonio ; Kamarashev, Jivko ; Kerl, Katrin ; Plaza, Tobias ; Metze, Dieter

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Cover letter AJD-D-12-00022 R1

Dear Dr. Sangüeza, dear Omar

Enclosed please find the revised manuscript " Primary cutaneous CD8+ small to medium-sized lymphoproliferative disorder in extrafacial sites - clinicopathological features and concepts on their classification" (AJD-D-12-00022). We are very grateful for your comments and the comments of the reviewers. Enclosed please find the point-by-point answers to their comments. The corresponding changes in the manuscript has been highlighted in red.

We hope that the revised manuscripts fulfills the requirements and very high standard for publication in the Journal. We very much appreciate your evaluation of our manuscript.

Yours sincerely,

Werner

Point-by-point answers to the reviewer's comments
Reviewer #1:

Reviewer #1: An excellent paper on an evolving topic. As more cases like these emerge, we will be able to say with more confidence where this entity lies along the PTCL, NOS spectrum.

1. Interesting that only one of three cases showed +clonality. the multiplicity of the lesions in case 1 suggests lymphoma as does dim cd3 in case 3 (i think cd3 is present but dim).
Reply: In fact a clonal T-cell population was found in two one of the three cases (Cases 2 and 3 - repeating the clonality assay in the biopsy of patient 3 revealed also clonal T-cells). This detection rate of clonality is very similar to the one in the CD4+ small/medium-sized T-cell lymphoma, which represents a form of analogon to our CD8+ cases (Beltraminelli et al. Am J Dermatopathol 2009). Moreover we agree with the reviewer that the occurrence of multiple and recurrent lesions, which only partially responded to radiotherapy and methotrexate, in Case 1 prove the diagnosis of a lymphoma.

2. Would have been very interesting to do ebv on case 3, especially with presence of numerous b cells. bcells in PTCL has been linked to ebv expression (mattoch et al., ajcp, 2009). these lymphomas are thought to represent secondary cutaneous disease but looks like in case 3, the course is indolent. i assume staging work up was negative?
Reply: We are grateful for this comment. We have performed in situ hybridization for EBV transcripts (EBER) and PCR for EBV DNA, which both were negative. The staging examinations were negative. This informations were added to th erevised manuscript in the section "Results".

3.I think in cases with documented small populations of cd4+ cells, that those may be background reactive cells. they may be small and angulated like the tumor cells.
Reply: We fully agree with the interpretation that the CD4+ T-cells represent background reactive cells.

4. Very interesting that lesional cells express granzyme but not tia1==may also be indicative of lymphoma.
Reply: We also interpret this finding as a further argument in favor of a lymphoma.

5. The manuscript should be proofed by a native english speaker. the figure legends should be expanded to include complete descriptive sentences about the figures. figures are very nice.

Reply: The manuscrript has been proofed by Dr. Walter Burgdorf, MD, who is a native English speaker and editor of several dermatology and dermatopathology books. Complete descriptive sentences were added to the figure legends.

Comment by the authors:
In addition, we have slightly changed the title and use the term "lymphoproliferative disorder" instead of "lymphoproliferation" since the first term is more consistent with the terminology used in current lymphoma classifications.

Abstract

Three cases with CD8+ small to medium-sized lymphoproliferations in the skin at extrafacial sites are described. Clinically, the patients presented with papulo-nodular or plaque-like lesions without preceding patches. Histopathologically, non-epidermotropic nodular or diffuse infiltrates were composed of small to medium-sized pleomorphic lymphocytes which expressed CD8 (more than 80% of the cells) and granzyme B (60-70% of the cells), but were negative for CD4, CD30 and CD56. There was no association with Epstein-Barr virus. A clonal T-cell population was detected in two patients. Staging examinations did not reveal extracutaneous involvement. The two patients with solitary lesions underwent complete remission after radiation therapy, whereas one patient developed multifocal lesions and several recurrences. These CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites may belong to a spectrum of a phenotypically and prognostically heterogeneous cutaneous small to medium-sized lymphoid proliferations which are characterized by an indolent course in most patients.

Primary cutaneous CD8+ small to medium-sized lymphoproliferative disorder in extrafacial sites - clinicopathological features and concepts on their classification

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Key words: CD8, extrafacial, lymphoproliferative, small to medium-sized, lymphoma, pseudolymphoma

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Abstract

Three cases with CD8+ small to medium-sized lymphoproliferations in the skin at extrafacial sites are described. Clinically, the patients presented with papulo-nodular or plaque-like lesions without preceding patches. Histopathologically, non-epidermotropic nodular or diffuse infiltrates were composed of small to medium-sized pleomorphic lymphocytes which expressed CD8 (more than 80% of the cells) and granzyme B (60-70% of the cells), but were negative for CD4, CD30 and CD56. There was no association with Epstein-Barr virus. A clonal T-cell population was detected in two patients. Staging examinations did not reveal extracutaneous involvement. The two patients with solitary lesions underwent complete remission after radiation therapy, whereas one patient developed multifocal lesions and several recurrences. These CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites may belong to a spectrum of a phenotypically and prognostically heterogeneous cutaneous small to medium-sized lymphoid proliferations which are characterized by an indolent course in most patients.

Key words cutaneous small to medium-sized pleomorphic T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, cutaneous peripheral T-cell lymphoma not otherwise specified, cytotoxic lymphoma, indolent CD8-positive lymphoid proliferation of the ear, pseudolymphoma

Introduction

In the recent literature, there have been several reports of unusual proliferations of CD8+ lymphocytes of the skin which posed diagnostic problems, especially with regard to their classification according to the currently used schemes, and particularly the WHO/EORTC classification of cutaneous lymphomas. (1), (2), (3), (4) Those cases clearly differed from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (CTCL), as well as from other lymphoma types with CD8 expression such as subcutaneous panniculitis-like T-cell lymphoma, and lymphomas with occasional expression of CD8 such as mycosis fungoides, cutaneous gamma/delta T-cell lymphoma, and extranodal NK/T-cell lymphoma, nasal type (5), (6), (7), (8) Cases in which the lesions were located on the face, often involving the ear have been referred to as "indolent CD8-positive lymphoid proliferation of the ear and face", respectively are characterized by nodular infiltrates of small to medium-sized CD8-positive lymphocytes. Only two patients with a nodular infiltrate of CD8+ small to medium-sized lymphocytes have been reported in extrafacial locations. (9), (10) A common clinical feature of the reported cases of CD8+ small to medium-sized lymphoid infiltrates was an indolent course, which is in contrast to a rare subset of peripheral CTCL, not otherwise specified (NOS) with a cytotoxic phenotype which usually follows an aggressive course. (11) Some authors feel that the infiltrates of CD8+ small to medium-sized lymphocytes cases are morphologically related to primary cutaneous small to medium-sized pleomorphic T-cell lymphoma (SMPTL) except for the fact that the small to medium-sized lymphocytes in SMPTL express CD4 (1), (2), (3), (4) Here we present the clinicopathological features of three cases of extrafacial proliferations of small to medium-sized CD8+ lymphocytes of the skin and discuss their possible categorization.

Material and Methods

A total of 6 biopsies from 3 patients were available for a histopathological review. Biopsy specimens were fixed in 10% buffered formalin and sections were routinely processed and embedded in paraffin. Serial 4 micrometer-thick sections were cut for hematoxylin and eosin stains as well as immunohistochemical stains. The antibodies used for immunohistochemistry included: CD2 (1:50, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD3 (1:75, Dako, Glostrup, Denmark), CD4 (1:2, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD7 (1:25, Dako, Glostrup, Denmark), CD8 (1:400, Dako, Glostrup, Denmark), CD20 (1:600, Dako, Glostrup, Denmark), CD30 (1:75; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD56 (RTU, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), and TIA-1 (1:50, Immunotech Marseille, France), as well as granzyme B (1:50; Dako, Glostrup, Denmark) and perforin (1:20; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), beta F1 (1:50, Thermo Scientific, Germany). Immunostaining was performed according to standard protocols using alkaline phosphatase-anti-alkaline phosphatase method, avidin-biotin complex or streptavidin-biotin complex labeled with peroxidase or alkaline

phosphatase. Appropriate positive and negative controls were applied. The antibody panel used differed in individual cases depending on the availability of the tissue/antibodies.

In all cases, molecular T-cell receptor (TCR) rearrangement studies were performed using a multiplex polymerase chain reaction (PCR) as described elsewhere. (12) Appropriate positive and negative controls were included in all analyses. Also, in situ hybridization for EBV was performed.

Results

Clinical data

Case 1. A 48-year-old man presented in June 2007 with an erythematous nodule (diameter 1cm) on the right buttock. He had Bruton X-linked agammaglobulinemia that had been treated with immunoglobulin substitution for the previous 21 years. The lesion was excised. Three years later in April 201, he developed infiltrated tan plaques on the dorsal aspects of the left foot and toes (Figure 1A). The working histopathologic diagnosis was "suspicious for cytotoxic lymphoma", so the patient was investigated to exclude extracutaneous disease (including peripheral blood studies and PET-CT), but no extracutaneous involvement was found. In May 2010 the lesions were treated with radiation therapy (total dose 32 Gy using 100kV) with complete regression. In March 2011 a relapse with a plaques on the left foot was observed (Figure 1B) which was treated again with radiation therapy (total dose 52 Gy using 40kV; March to June 2011) which again resulted in complete regression. Three months later, the patient developed the second recurrence of small livid papules on the left foot adjacent to the radiation site and in addition 3 small papulo-nodular lesions (diameter up to 8mm) in the right retroauricular area. The staging examinations (peripheral blood studies, PET/CT) were repeated and were once again negative. In parallel to the superficial X-ray irradiation for the retroauricular lesions, treatment with low-dose methotrexate (15mg/week) was started in November 2011 and resulted in complete remission until last follow-up in January 2012. Several biopsies of the lesions on the right buttock, the lesions on the feet and the retroauricular papulo-nodular lesions were histologically examined.

Case 2. An 87-year-old woman presented with a solitary, red infiltrated non-scaling plaque (diameter 5 cm) on the right lower leg (Figure 2). Her medical history was unremarkable for skin or neoplastic diseases. The clinical examination did not reveal enlarged lymph nodes. The lesion was treated by radiation therapy (total dose 50 Gy). No recurrence was observed during follow-up of 2 years.

Case 3. A 52-year-old man presented with a 1.3x0.8 cm solitary nodule on the right shoulder. The lesion was completely excised. The staging examinations did not reveal any extracutaneous involvement. One year later, there was no evidence of cutaneous and extracutaneous disease. Blood examinations revealed a mild lymphocytosis, but no atypical lymphocytes. All findings were normal at the last follow-up 26 months after diagnosis.

Histopathologic, immunophenotypic and molecular findings

Common to all cases was a dense nodular to diffuse dermal infiltrate composed mainly of small and medium-sized lymphocytes were found which were separated from the overlying epidermis by a variably thick Grenz zone (Figures 1C, 3A and 3B). The epidermis was either normal or focally atrophic with a loss of the undulated pattern. Specifically, no epidermotropism was observed in any of the biopsies of all three patients (Figure 3B). In all biopsies, the small to medium-sized lymphocytes showed chromatin dense nuclei with mild to moderate nuclear pleomorphism with cleaved nuclei (Figures 1D and 3C). A few eosinophilic granulocytes were admixed. In patient 1, several biopsies showed a granulomatous component with numerous histiocytes occasionally forming small epithelioid granulomas in addition to the lymphocytic infiltrate (Figure 1E). In addition, the lymphocytic infiltrates were centered on a slightly hyperplastic hair follicle but there was no folliculotropism in one of the biopsies of the acral lesions in patient 1 (Figure 1C).

Immunohistochemically, the small to medium-sized lymphocytes were strongly positive for CD8, with about 80-90% of the cell population staining for this marker in each specimen (Figures 1F, 3D and 3E) (Table 1). A minority of the small lymphocytes (10-30% of the cells) expressed CD4 (Figures 1G and 3F). The cells expressed other T-cell markers (CD2, CD3 [except for patient 3], CD5 and CD7) and were positive for betaF1 (Figure 3G). The CD8+ lymphocytes were negative for TIA-1, but granzyme B was expressed by 60-70% of the small to medium-sized lymphocytes in the biopsies of patient 1 and 2. In the biopsies of all patients, the lymphocytes were consistently negative for CD30 and CD56. There was an admixture of scattered medium-sized B-cells in the biopsy of patient 3. Less than 10 percent of the small to medium-sized CD8+ lymphocytes displayed proliferative activity in the Ki67/MIB-1 staining (Figure 1H). In the two patients (patients 1 and 3), from whom multiple biopsied were studied, the immunoprofile of the lymphoid cells was identical in each specimen. In situ hybridization for EBV RNA (EBER) performed in biopsies of all patients were negative.

Molecular biological T-cell clonality analyses revealed a clonal T-cell population in the biopsy of patient 2 and patient 3, whereas the infiltrates in the patient 1 were polyclonal (Table 1).

Discussion

The common clinicopathological features to all our cases are papulo-nodular or plaque-like lesions without preceding patches and histologically nodular proliferations of small to medium-sized CD8+ lymphocytes lacking epidermotropism. In the context of cutaneous lymphoid infiltrates, cases showing a cytotoxic phenotype should always alert the pathologist to a possibility of an aggressive cutaneous lymphoma but the lesions in our three patients are clearly different, both clinically and histopathologically, from aggressive cytotoxic lymphomas such as primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma and other aggressive lymphoma type in which CD8 expression is commonly or occasionally observed such as subcutaneous panniculitis-like T-cell lymphoma, cutaneous gamma/delta T-cell lymphoma, and

extranodal NK/T-cell lymphoma, nasal type. (13), (14), (15) CD8 phenotype has rarely been observed in less aggressive or rather indolent CTCL including mycosis fungoides, pagetoid reticulosis and CD30+ anaplastic large cell lymphoma. (16), (17), (18), (19) A cytotoxic infiltrate has recently been found in peculiar form of lupus erythematosus which showed overlapping clinicopathological features of subcutaneous panniculitis-like T-cell lymphoma and lupus erythematosus. (20) All of the above diagnoses were clearly excluded in our patients. In particular, the lack of epidermotropism in all biopsies and the absence of preceding patches argue against CD8+ variant of MF as well as primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. Cutaneous gamma/delta lymphoma is excluded by the presence of beta F1 expression. The indolent clinical course and the lack of association with EBV exclude extranodal NK/T-cell lymphoma.

Histopathologically, our cases are very similar to those reported as indolent CD8+ lymphoid proliferation of the ear (or face) but in all of our patients the lesions were located in extrafacial sites. So far, 5 patients (including our 3 patients) with CD8+ small/medium-sized lymphoid infiltrates at extrafacial sites have been reported (9), (10) Their clinicopathologic features are summarized in Table 1. Clinically and histologically our cases are very similar or even identical to the patient reported by Khamaysi et al which was interpreted by the authors as CD8+ small to medium-sized pleomorphic CTCL. (10) Classification of the CD8+ lymphoid infiltrates in our cases is challenging. Although the term cutaneous peripheral T-cell lymphoma, NOS (PTL, NOS) can be applied to cases which do not fit into any of the well-defined forms of CTCL and CD8 phenotype has indeed been observed in peripheral T-cell lymphoma, NOS, including cases with small to medium-sized cytomorphology, such tumors usually run an aggressive clinical course. In a large study, cytotoxic phenotype was found in about 15% of peripheral T-cell lymphoma, NOS, and a median survival of the affected patients was 28 months. (11) Clinically, our cases show a similar biological behavior as seen in CD4+ SMPTL which manifests in the vast majority of the patients with solitary or grouped plaques or nodules and runs an indolent course with an excellent prognosis (11), (21). Therefore our cases could be regarded as a phenotypic CD8+ lymphoproliferative analogue to the CD4+ SMPTL (Figure 4). The presence of small and medium-sized lymphocytes with nuclear atypia, the detection of clonal T-cells in two of three cases and the relapses in one of the patients are in favor of a lymphoma.

In regard to the indolent course and the overlapping histological features, some authors have indicated that CD4+ SMPTL cannot be distinguished with certainty form nodular pseudo-T-cell lymphoma and therefore proposed the term "cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance (21), (22). In fact, some cases of pseudolymphoma composed of small and occasional medium-sized cells may be overdiagnosed at present as small to medium-sized pleomorphic T-cell lymphoma. (21), (23) Moreover, a CD8 phenotype has been reported in rare cutaneous pseudolymphomas in HIV-positive patients and other conditions characterized by lymphoid infiltrates, including lymphoid infiltration of Jessner-Kanof and

palpable arciform migratory erythema (24), (25), (26) These lesions feature a less prominent infiltrate composed almost exclusively of small cells. The possibility that the infiltrate in our patient 3 represents a form of pseudolymphoma (reactive lymphoid hyperplasia) cannot be totally refuted. The history did not indicate a drug-related form of pseudolymphoma as no association with drug intake had been reported by the patient. In addition, the lack of CD3 expression by the small to medium-sized tumor cells in case 3 argues against pseudolymphoma.

Patients with SMPTL appear to have a favorable prognosis independent of their CD4 or CD8 - positive phenotype, especially those with a solitary lesion (10), (27), (9), (23) Nevertheless, the relapsing course and the multifocal occurrence of tumors in patient 1 may indicate that the extrafacial CD8+ lymphoid proliferations are a prognostically heterogenous group, as the same course also been reported in CD4+ SMPTL. In the latter entity, cases with multiple rapidly growing tumors and a high proliferation rate may run a more aggressive course. (28) Thus a patient with multiple lesions should be followed more intensively and may require more intense treatment.

A surprising feature observed in one case (Case 1) was the conspicuous granulomatous infiltration in the first biopsy. In the context of cutaneous lymphomas, granulomatous features are typically present in granulomatous slack skin and granulomatous mycosis fungoides and are rare in other lymphoma types. (29), (30), (31), (32) They have also been described in pseudolymphomatous folliculitis, a term used to describe a distinctive pattern seen in both lymphomas and pseudolymphomas. (33), (34) Along this line, some cases of "pseudolymphomatous folliculitis" and small to medium-sized pleomorphic CTCL show a great clinicopathological overlap. (34), (35), (36) In our patient with Bruton X-linked agammaglobulinemia, the granulomatous (and lymphomatous) infiltrate may be related to immunodeficiency or immunoglobulin substitution. Similar histopathological findings have recently been reported in a Japanese patient with X-linked agammaglobulinemia, including a heavy small to medium-sized non-epidermotropic lymphoid infiltrate with cytotoxic CD8+ phenotype and a great admixture of histiocytes. (37) The tumor was classified as peripheral CTCL, NOS and the patient clinically presented with multiple papules, macules and patches on the face and trunk. (37)

In conclusion, we report a series of CD8+ small to medium-sized cell lymphoid proliferations of the skin with an indolent behavior similar to those reported for CD8+ lymphoid proliferation on the ear and face, but all occurring in extrafacial sites. Further observations are needed collect a larger number of such cases in order to get insight into the biologic nature of the lesion - lymphoma or reactive process-and to find out whether they represent a prognostically heterogeneous group of lesions. If such lymphoid proliferations should be classified as lymphoma, then according to the currently used schemes (WHO classification, 2008, 4th edition) they would conform to the concept of cutaneous PTL, NOS and could perhaps be regarded as the

CD8+ analogue of CD4+ SMPTL within a larger spectrum of nodular infiltrates of small to medium-sized pleomorphic lymphocytes (Figure 4). We propose the term primary cutaneous CD8+ small to medium-sized lymphoproliferative disorder. A growing body of evidence suggests that what is now called small to medium-sized pleomorphic CTCL may in fact represent a phenotypically and prognostically heterogeneous group of lymphoid proliferations. (28)

Acknowledgments

We are grateful to Professor Günter Burg, MD, Zürich (Switzerland) and to Prof. Helmut Kerl, MD, Graz (Austria) for the helpful discussion of the three cases, and Dr. Anja Wysocki, Dept. of Dermatology, Kantonsspital Lucerne, for clinical information on patient 2.

Figures

Figure 1: Patient 1 - Clinicopathologic findings

Fig. 1A: A scaly brownish plaque on the left foot was present at initial presentation.

Fig. 1B: Relapse with erythematous papules developed adjacent to the site of previous radiation therapy.

Fig. 1C: Superficial and deep nodular and confluent infiltrates were present in all dermal layers. H&E, original magnification X20

Fig. 1D: The infiltrates consisted of small to medium-sized pleomorphic lymphocytes with chromatin dense nuclei, H&E, original magnification X400

Fig. 1E: There is a granulomatous component with sarcoid-like granulomas and numerous small to medium-sized lymphocytes with nuclear atypia. H&E, original magnification X200,

Fig 1F: CD8 (red) is expressed by more than 80% of the small to medium-sized lymphocytes. Immunohistochemistry, original magnification X200.

Fig 1G: Only small lymphocytes accounting for less than 20% of the infiltrate express CD4. (red). Immunohistochemistry, original magnification X200.

Fig 1H: Proliferative activity is found in less than 10% of small to medium-sized pleomorphic lymphocytes.

Figure 2: Patient 2 - Erythematous plaque on the right lower leg

Figure 3: Patient 3 - Histological and phenotypic findings

Fig 3A: Superficial and deep nodular infiltrates were found in all dermal layers. H&E, original magnification X20

Fig. 3B: The lymphocytic infiltrates were separated from the overlying epidermis by an infiltrate-free Grenz zone. H&E, original magnification X200

Fig. 3C: The infiltrates consisted of small to medium-sized pleomorphic lymphocytes, H&E, original magnification X400

Fig. 3D: CD8 (red) is expressed by nearly all lymphocytes. Immunohistochemistry, original magnification X100.

Fig. 3E: CD8 (red) is expressed by more than 80% of the small to medium-sized pleomorphic lymphocytes. Immunohistochemistry, original magnification X200.

Fig. 3F: Expression of CD4 (red) is found by less than 10% of the small to medium-sized pleomorphic lymphocytes. Immunohistochemistry, original magnification X200.

Fig 3G: Less than 25% of the small to medium-sized pleomorphic lymphocytes express CD3 (red). Immunohistochemistry, original magnification X200.

Figure 4: Concept on the relationship between primary cutaneous small to medium-sized T-cell lymphoma with CD4+ or CD8+ expression, cutaneous CD8+ lymphoid proliferation of the ear / face and nodular pseudo-T-cell-lymphoma.

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Table 1. The main clinicopathological features of cutaneous CD8+ small to medium-sized lymphoid proliferations in extrafacial sites

Case	Sex/Age	Location	Clinical features	Treatment Follow-up	Histology	IHC	TCR
Case 1	M/48	Buttock (2007) Lower leg (2010)	Multiple infiltrative papules and plaques	Radiation therapy, Methotrexate (low-dose) Alive with disease (FU: 48 months)	Nodular infiltrate Small to medium-sized cells; no epidermotropism Granulomatous reaction in one specimen	CD2+, CD3+, CD4 (30%), CD5+,CD8 (80%), CD30-, CD56-, granzyme (70%), perforin -TIA1 (890%)	Negative
Case 2	F/87	Lower leg	Red infiltrated plaque	Radiation therapy Complete remission (FU: 24 months)	Diffuse infiltrate Small to medium-sized cells; no epidermotropism	CD2+, CD3+, CD4 (30%), CD5+, CD7+ CD8 (80%), CD30-, CD56-, granzyme B (60%), perforin -, TIA1 (70%)-	Positive
Case 3	M/54	Shoulder	1.3x0.8 cm solitary nodule	Surgical excision Complete remission (FU: 28 months)	Nodular infiltrate Small to medium-sized cells; no epidermotropism	CD3-, CD4 (10%), CD5+, CD8 (90%), CD30-, CD56-	Positive
Case reported by Khamaysi et al 2006	F/55	Right foot	Erythematous nodule (diameter 2cm)	Radiation therapy and surgical excision No FU available	Lichenoid infiltrate Small to medium-sized cells; no epidermotropism	CD3+, CD8+ CD4- CD20. CD30-, CD56-	Positive
Case reported by Friedmann et al. 1995	F/57	Widespread lesions	Tumors and nodules	Mechlorethamine, radiation therapy, Psoralen-UVA (PUVA), Interferon-alpha (FU: no evidence of disease at 86 months)	Small to medium-sized cells; no epidermotropism	CD3+ ,CD8+ (50-75%) CD4 (<25%) CD5+, CD7- CD30- CD20 (<25%)	Positive

Legend: FU: Follow-up; ND: not done; NR: not reported

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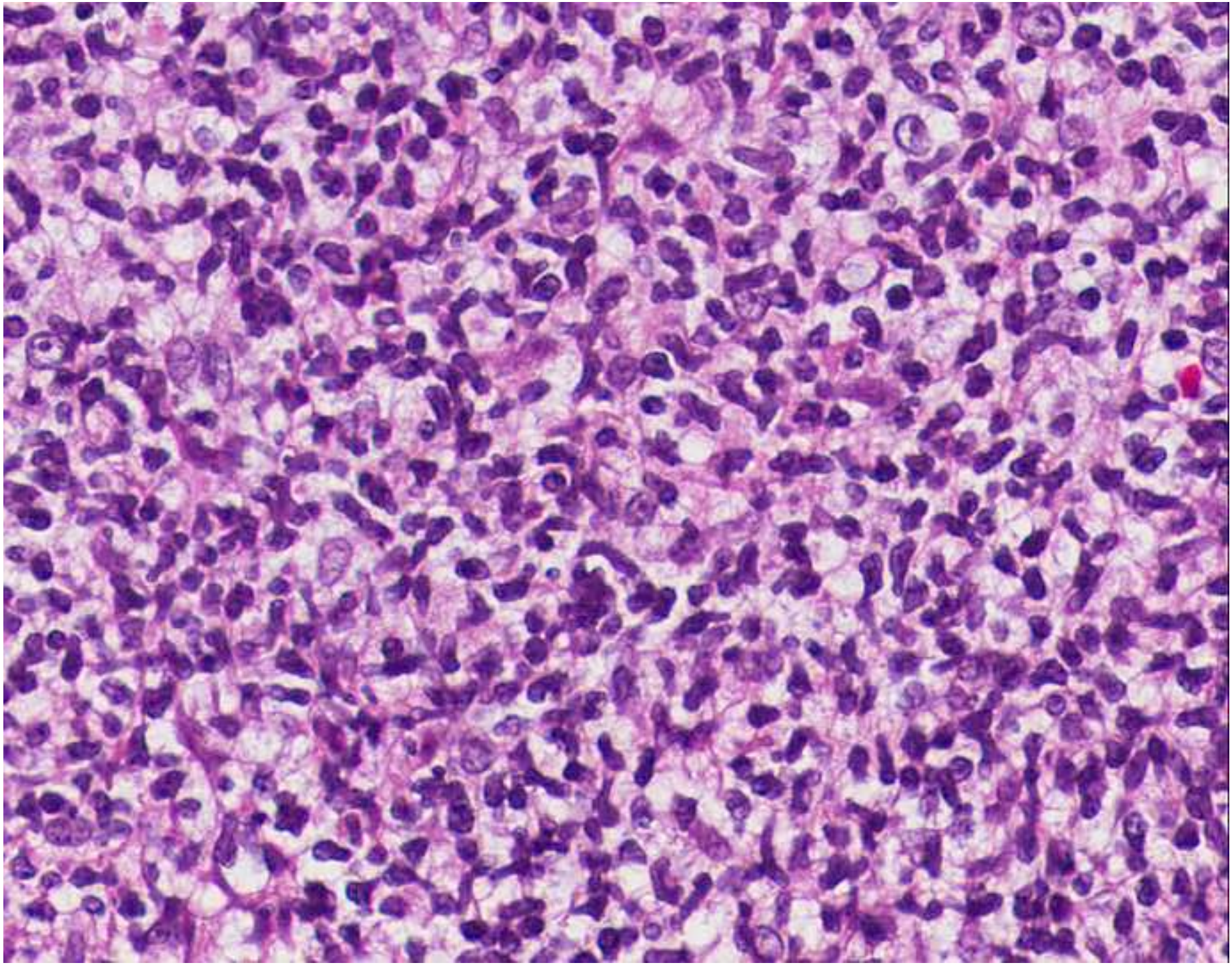

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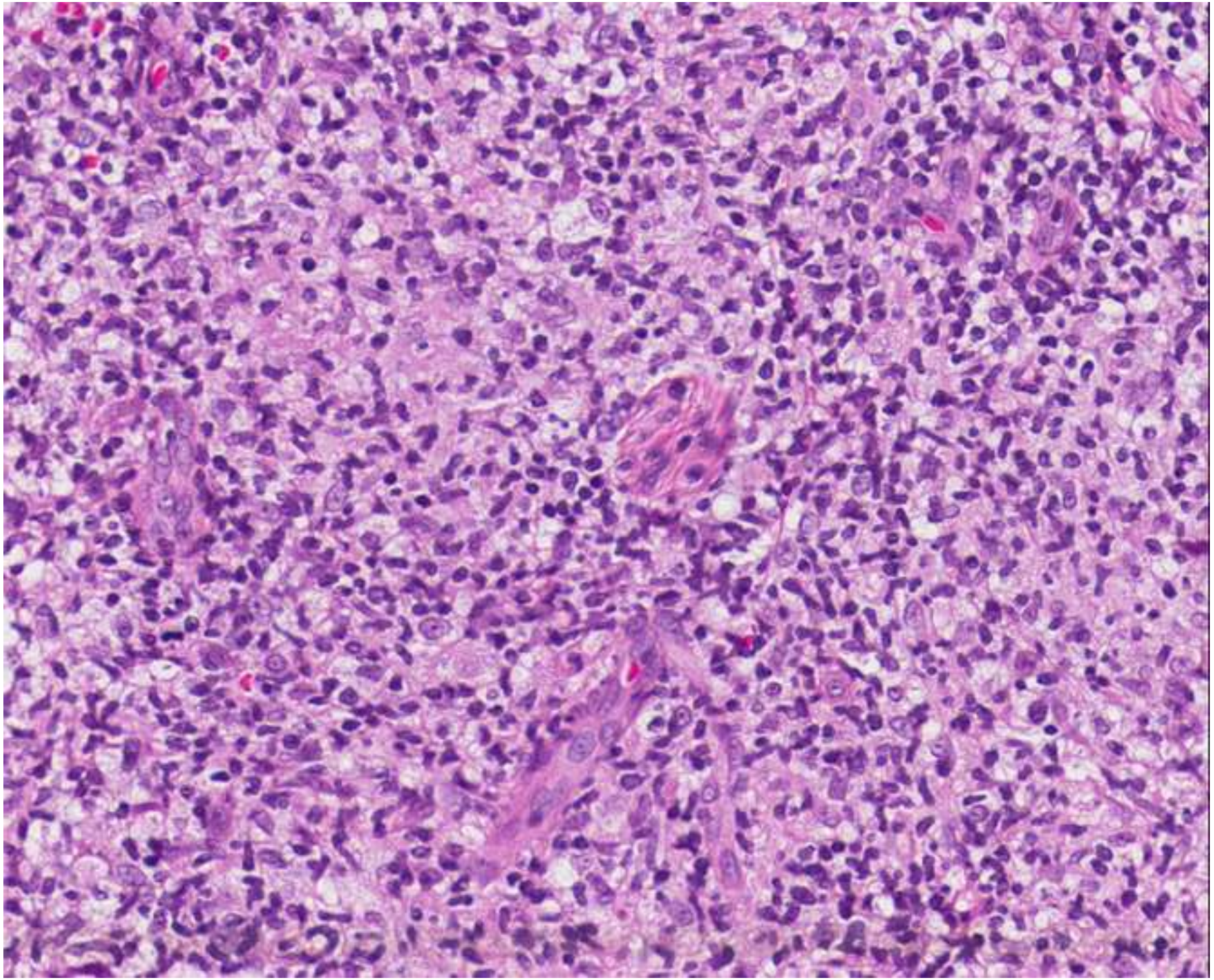

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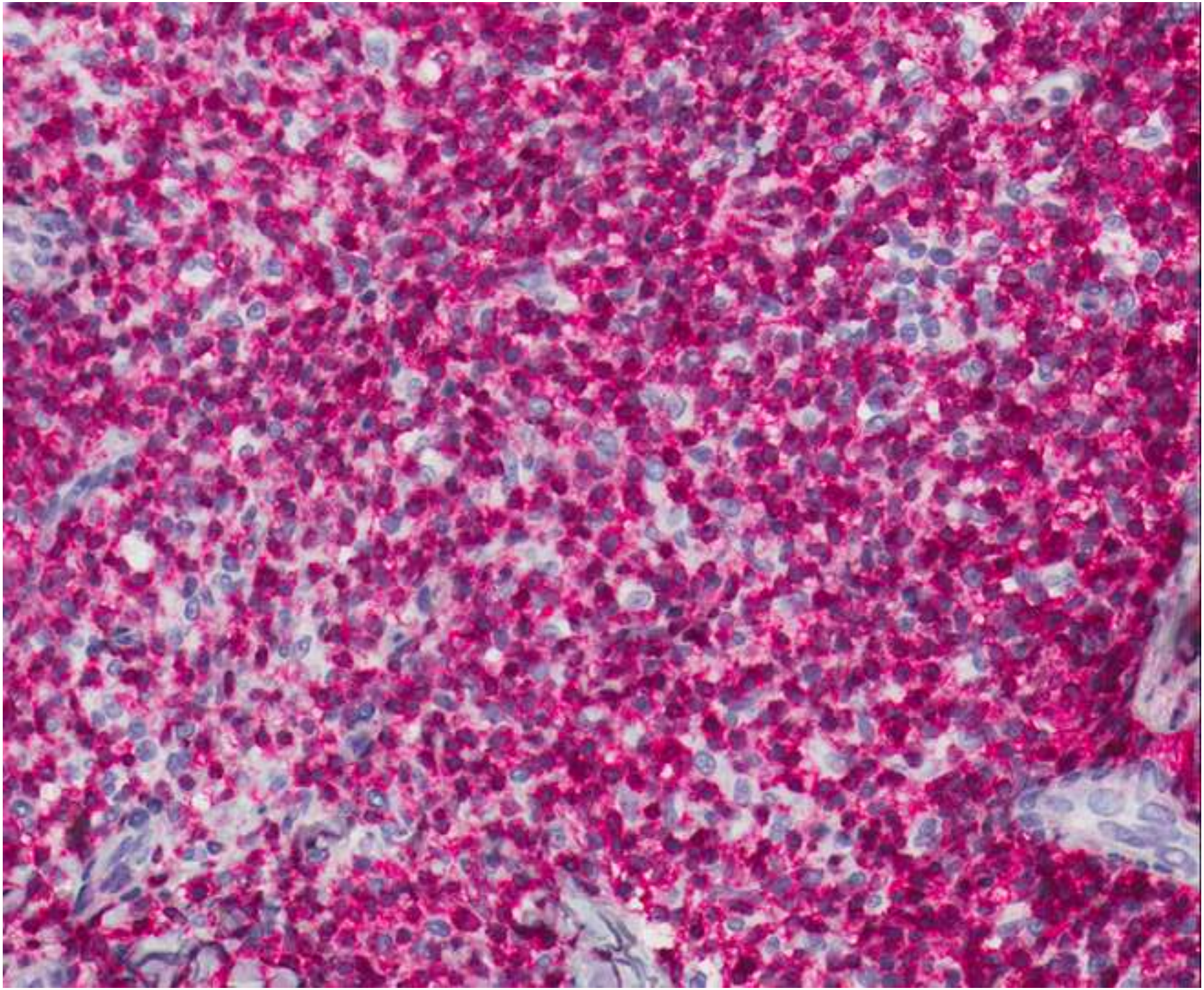

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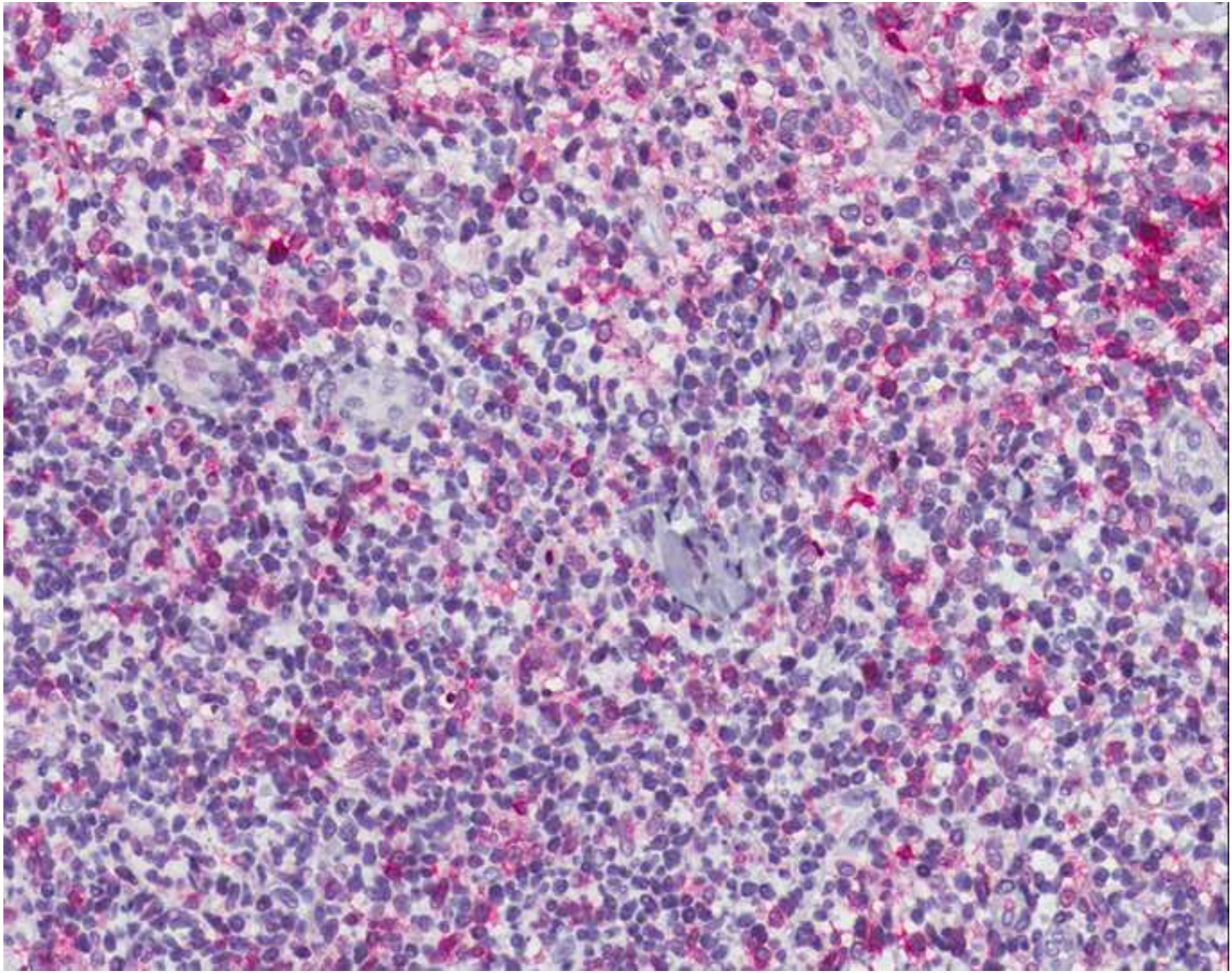

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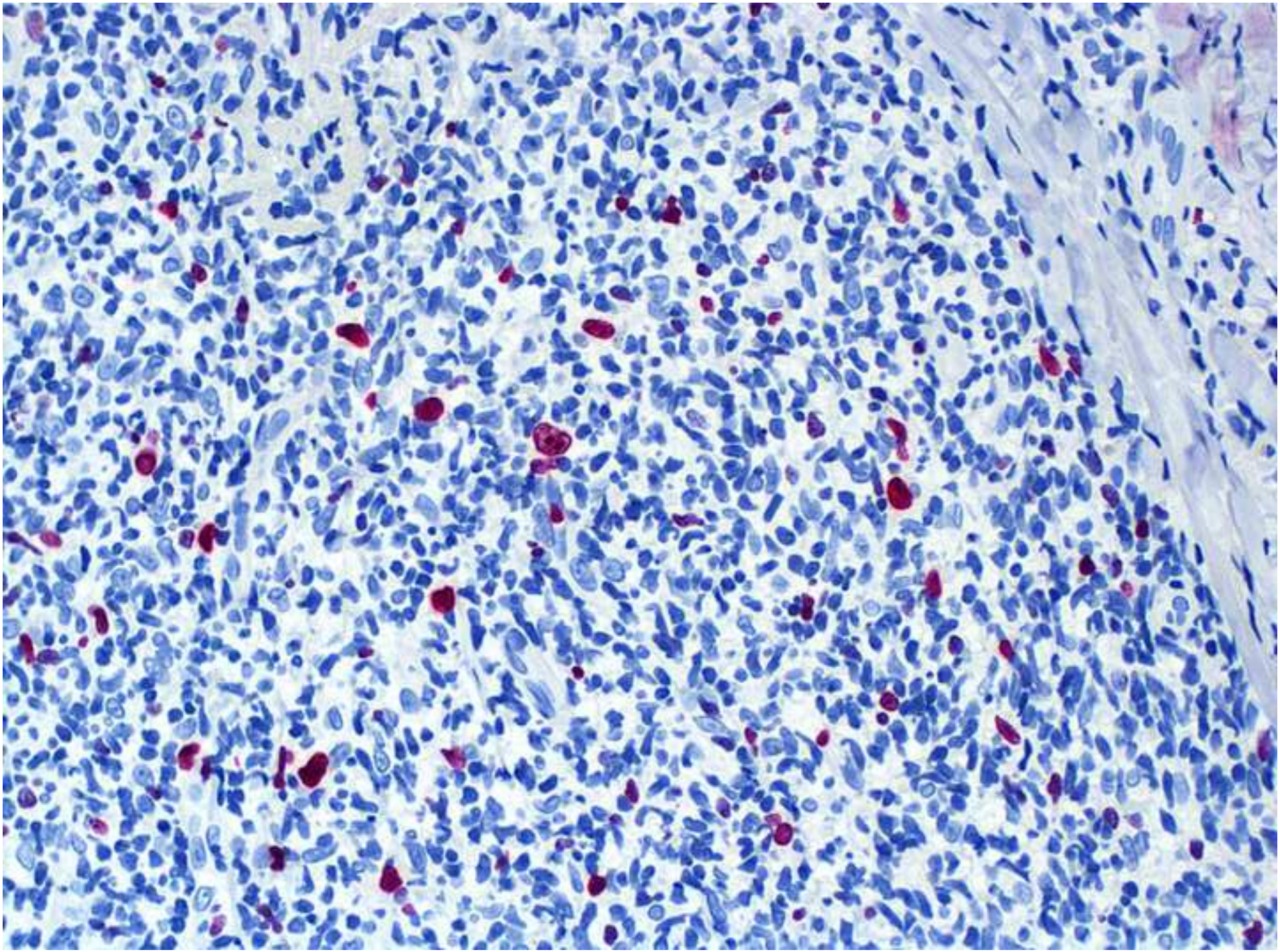

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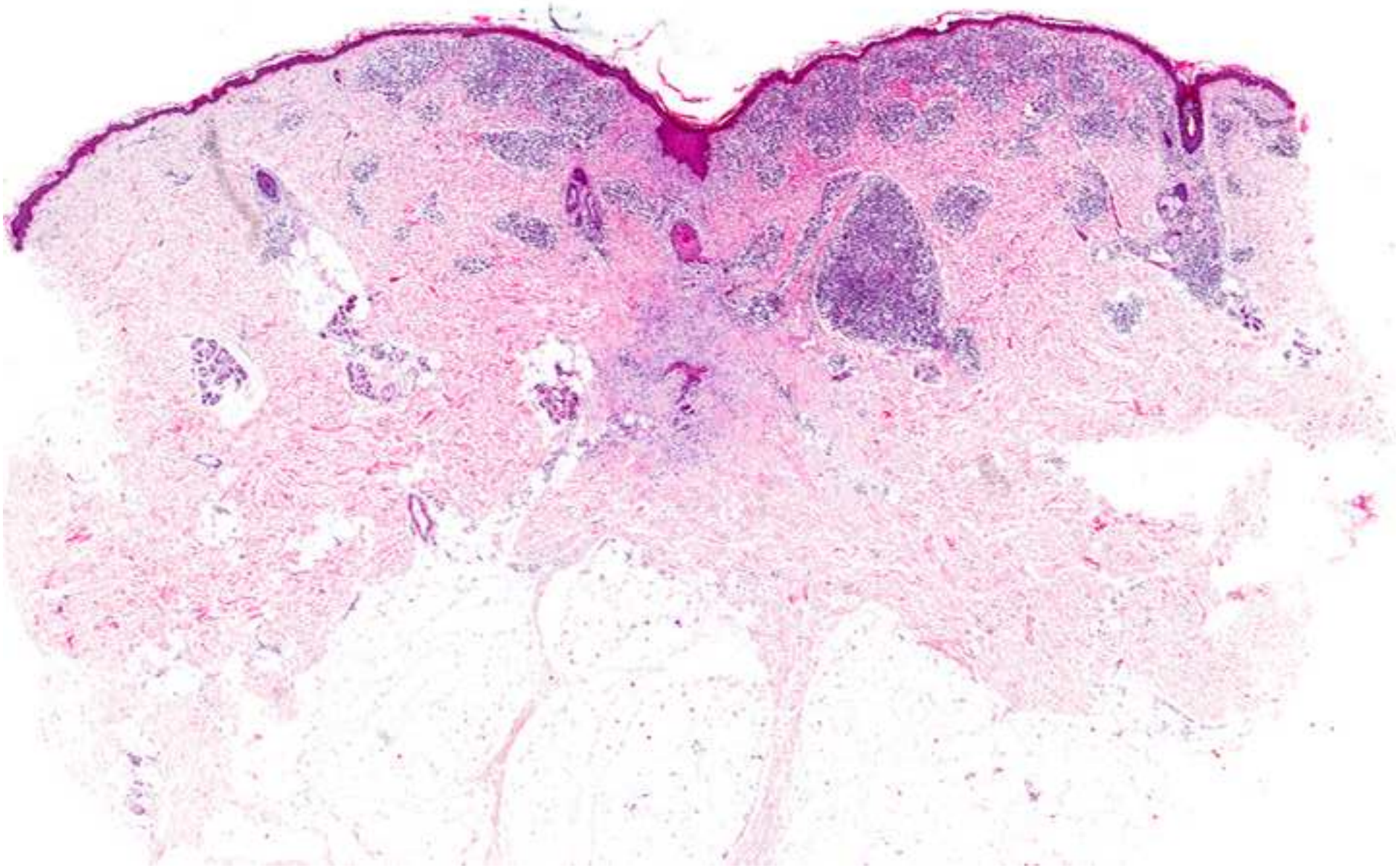

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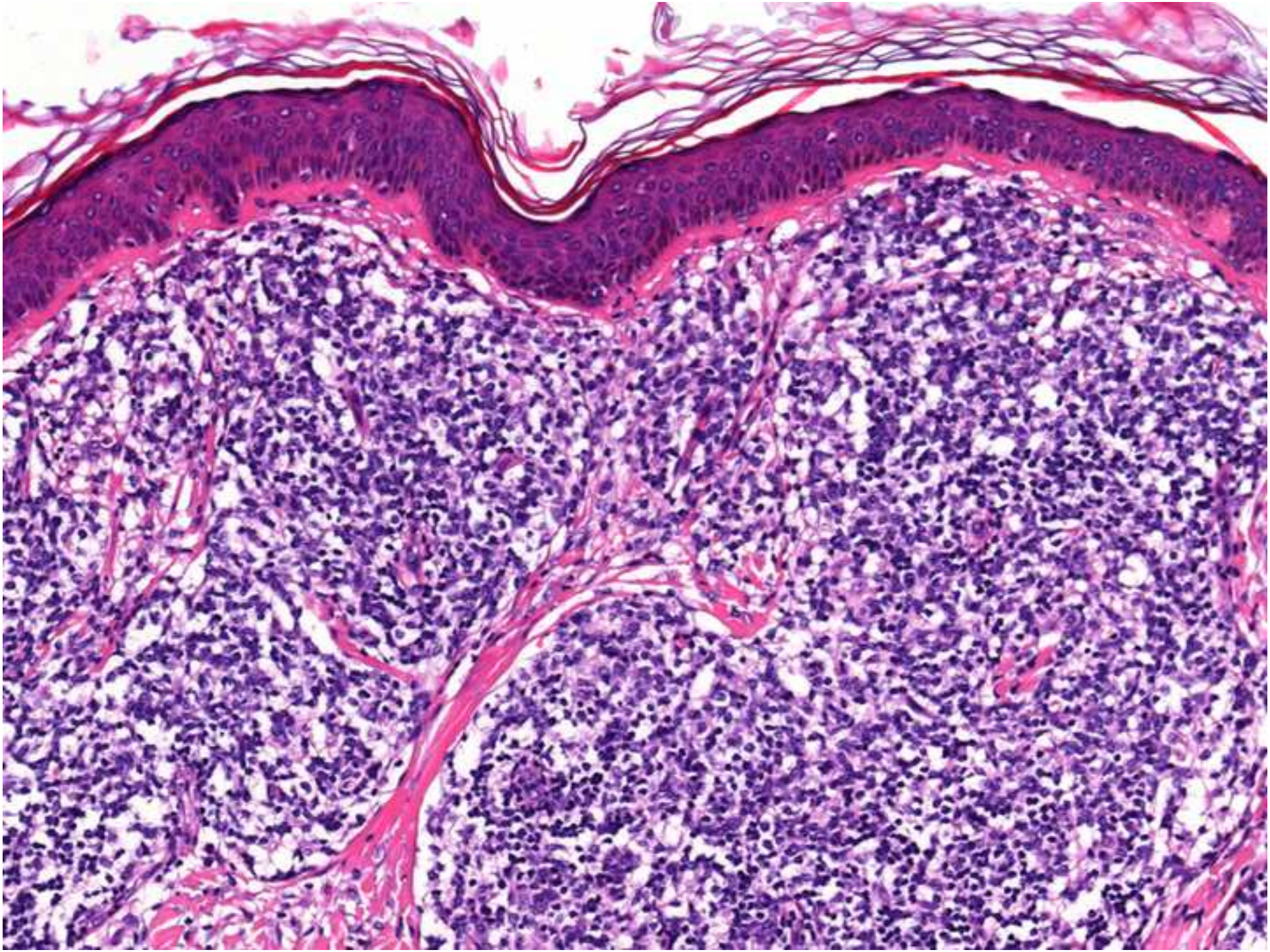

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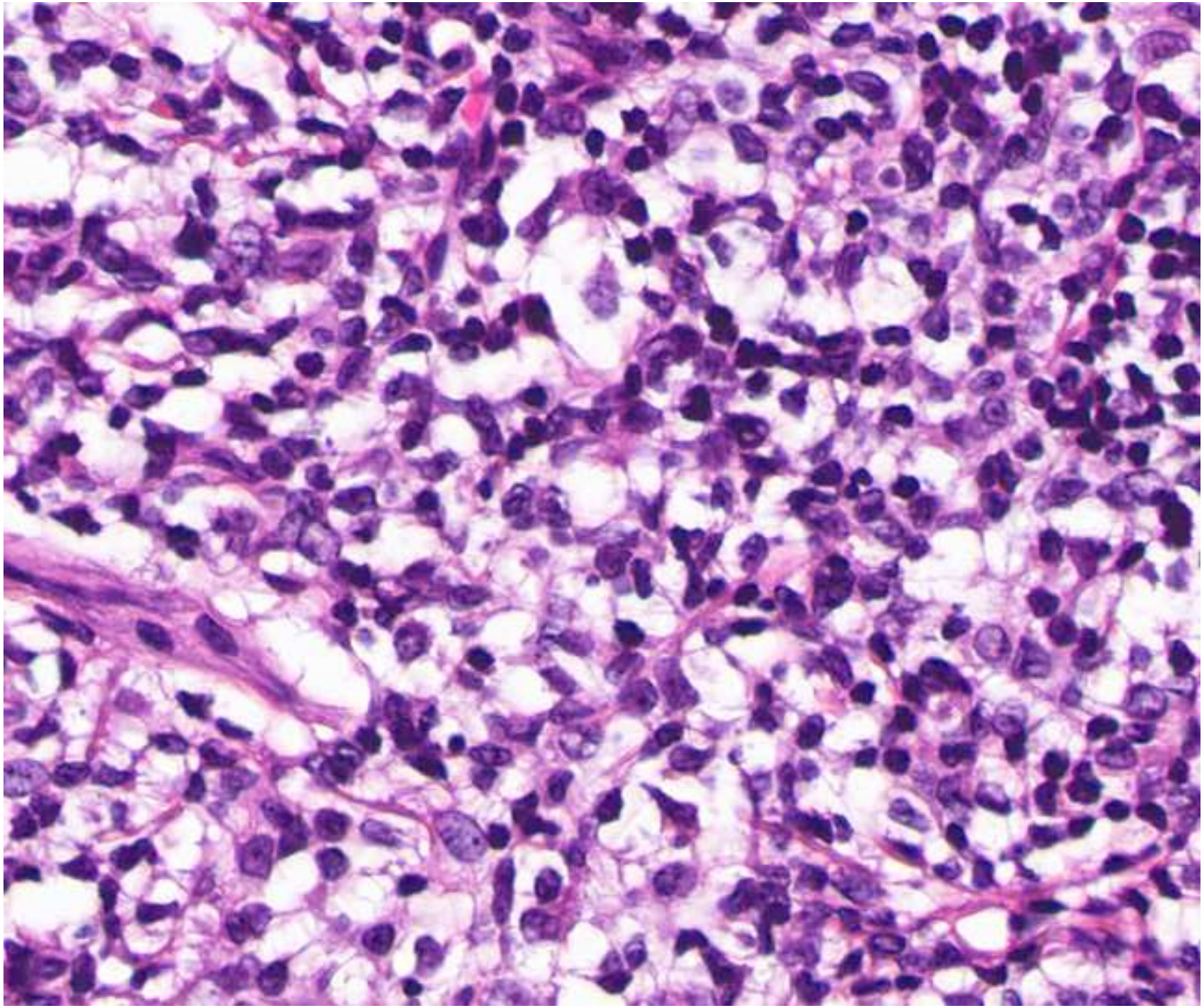

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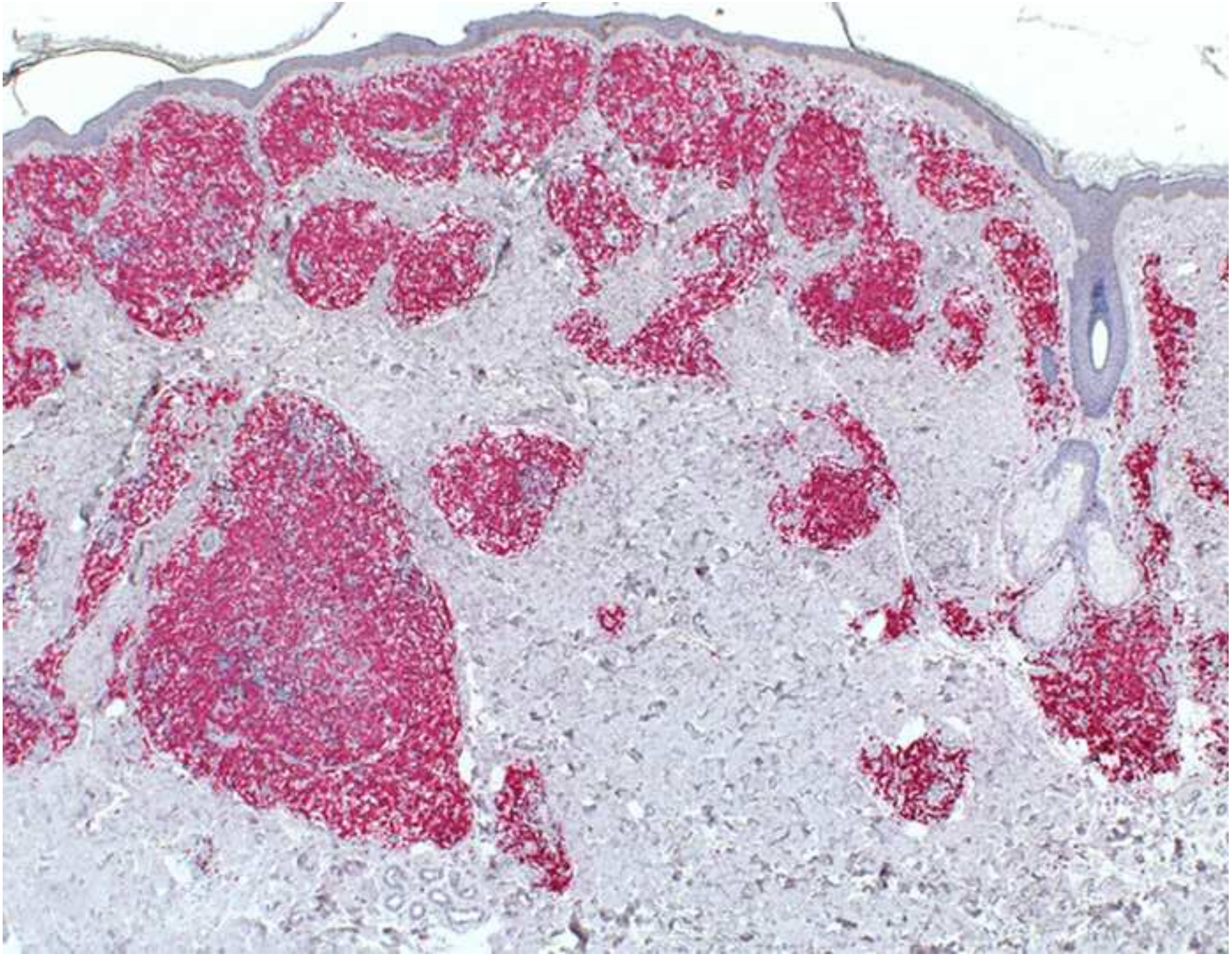

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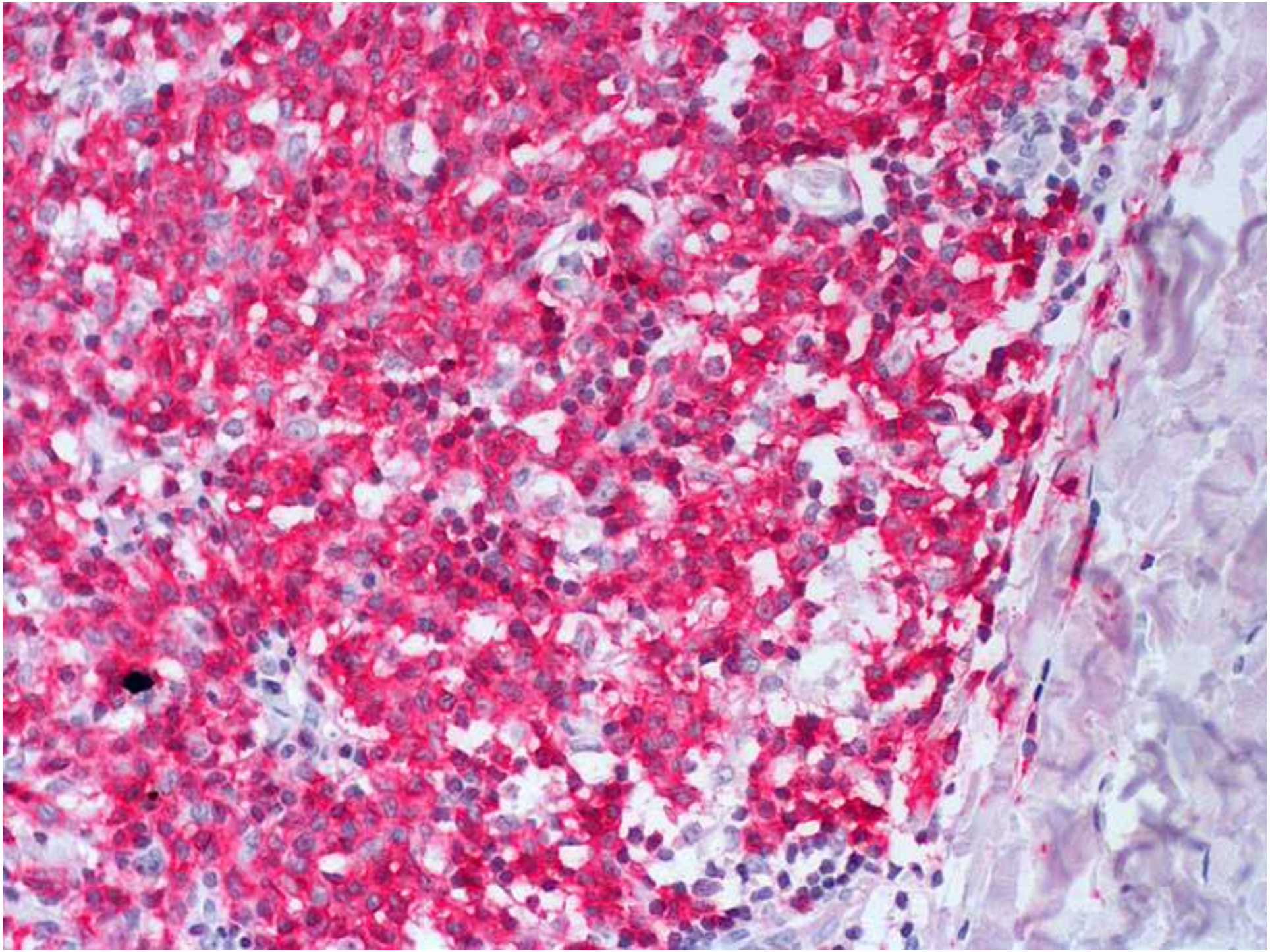

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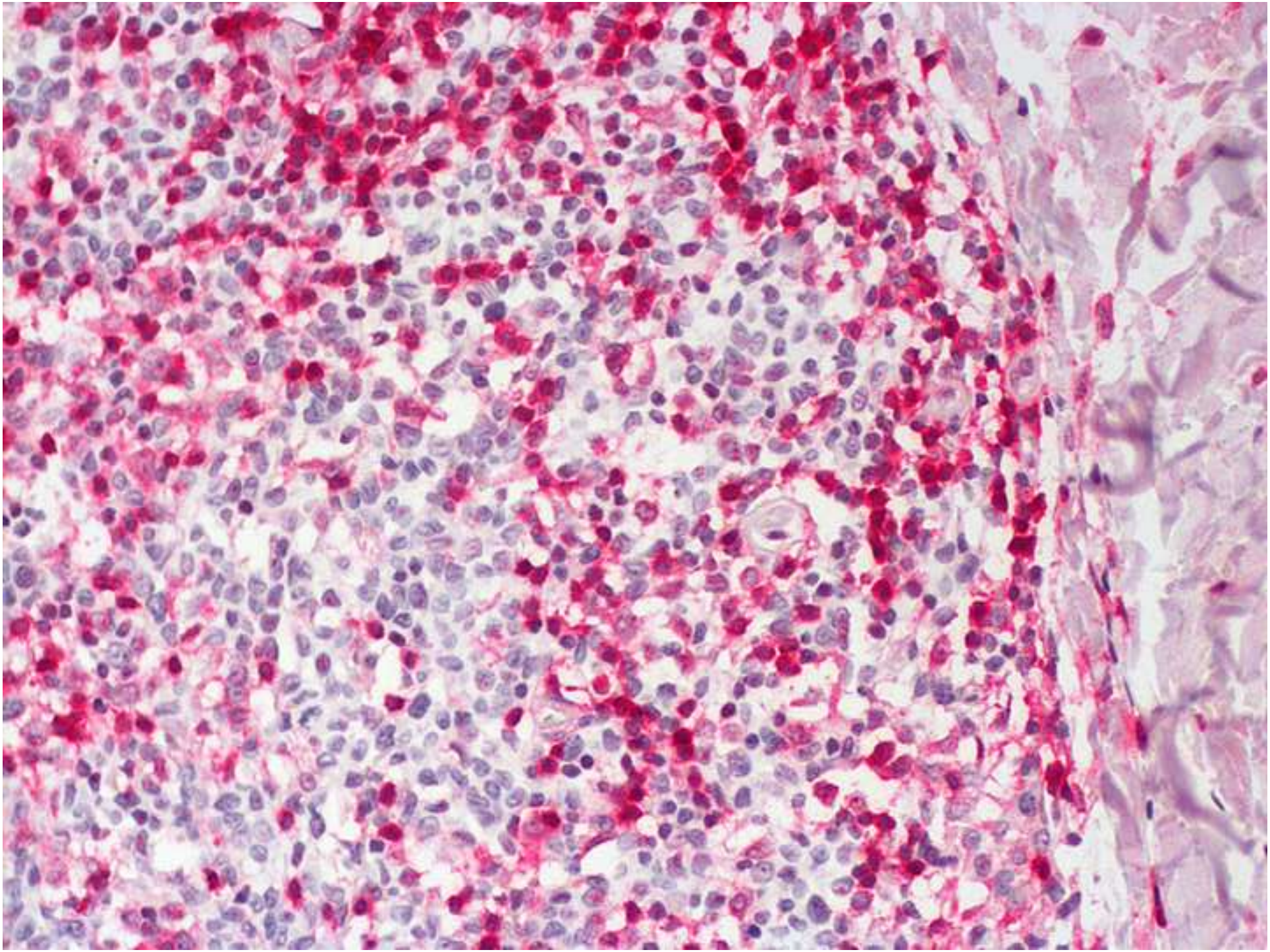

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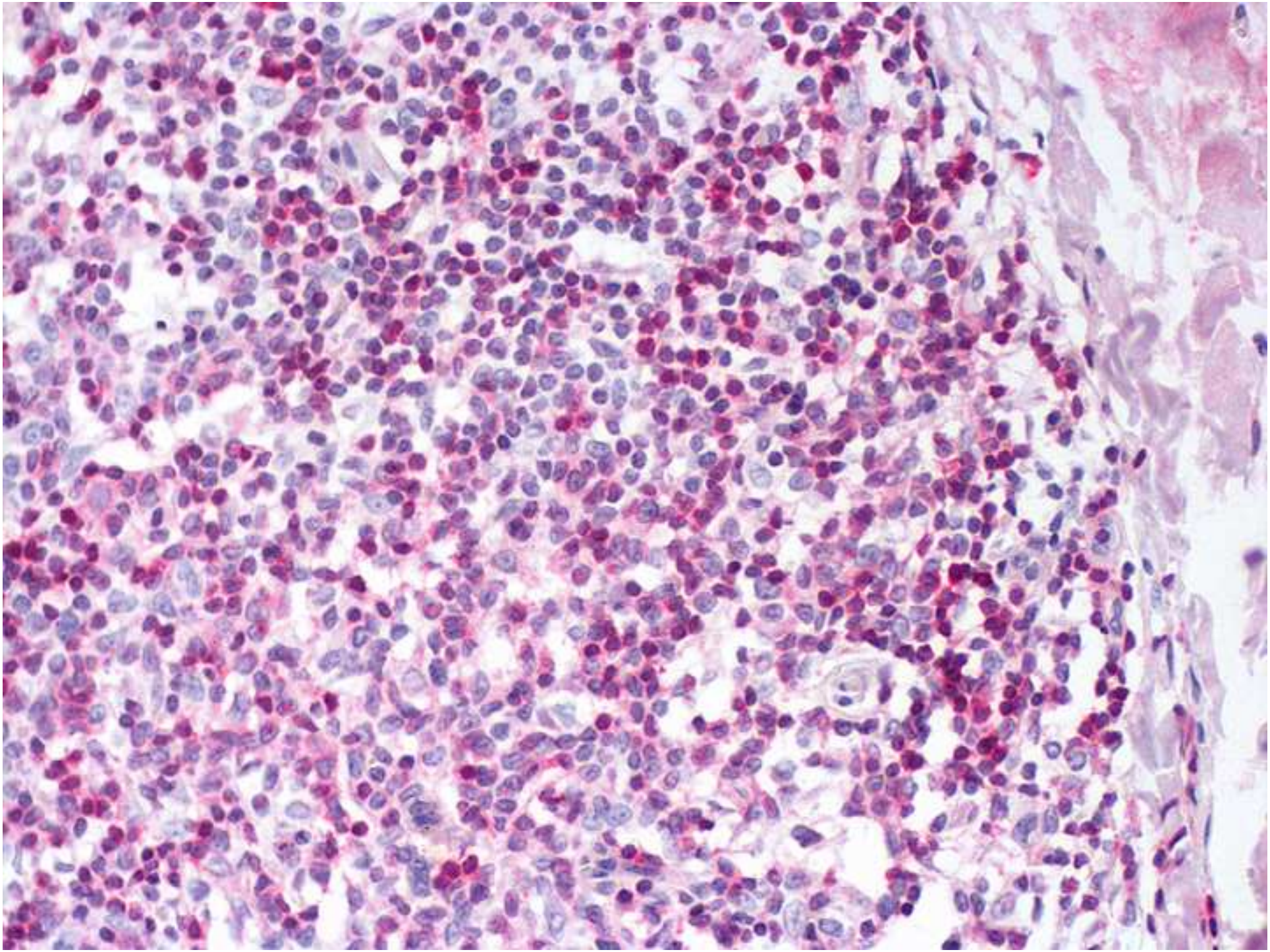

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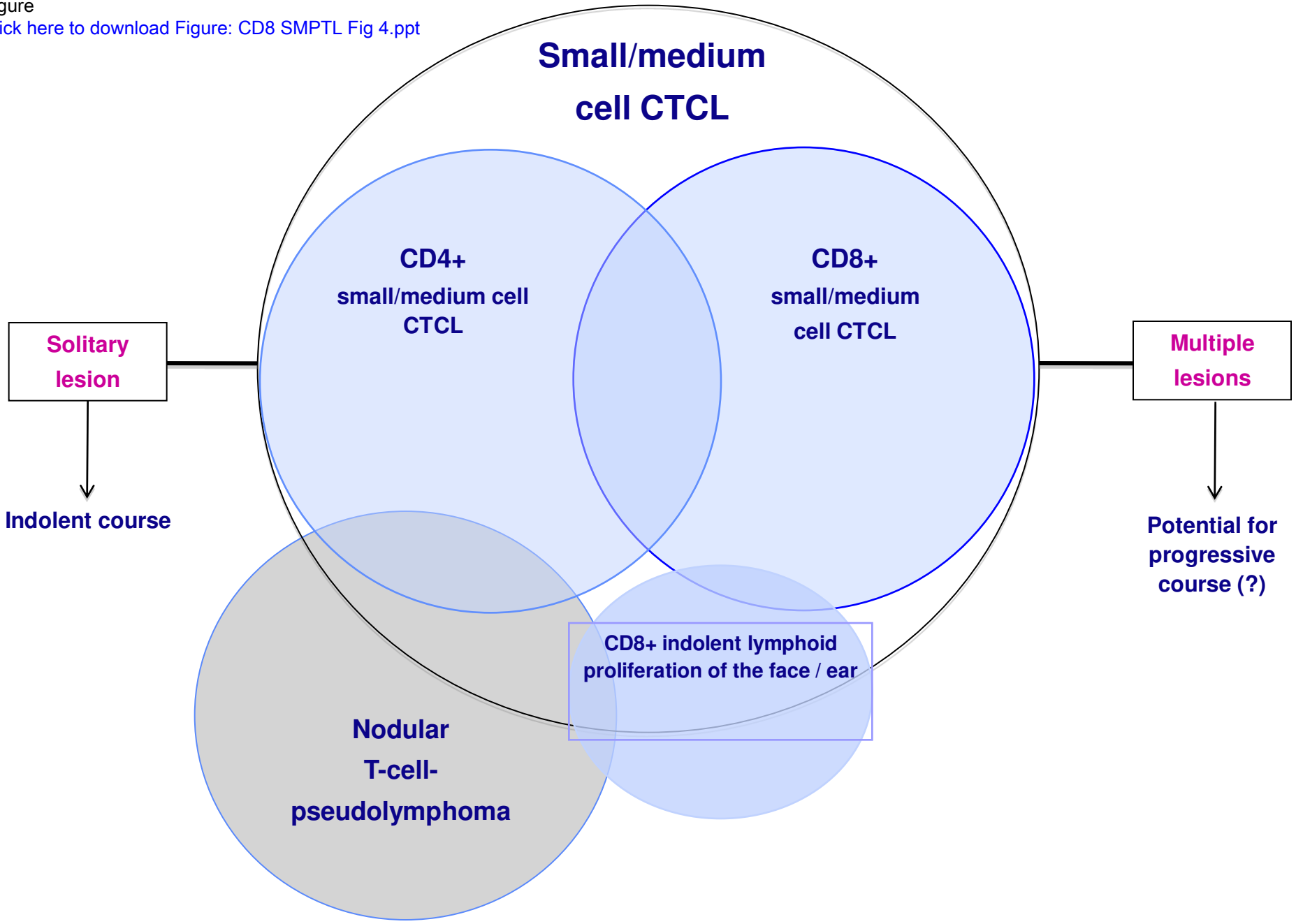

Abstract

Three cases of CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites are described. Clinically, the patients presented with papulo-nodular or plaque-like lesions without preceding patches. Histopathologically, non-epidermotropic nodular or diffuse infiltrates were composed of small to medium sized pleomorphic lymphocytes which expressed CD8 (more than 80% of the cells) and granzyme B (60-70% of the cells), but were negative for CD4, CD30 and CD56. There was no association with Epstein-Barr virus. A clonal T-cell population was detected in one patient. Staging examinations did not reveal extracutaneous involvement. The two patients with solitary lesions underwent complete remission after radiation therapy, whereas one patient developed multifocal lesions and several recurrences. The CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites may belong to a spectrum of a phenotypically and prognostically heterogeneous cutaneous small to medium-sized lymphoid proliferations which are characterized by an indolent course in most patients.

CD8+ small to medium-sized lymphoproliferations of the skin in extrafacial sites - clinicopathological features and concepts on their classification

Cover letter

Dear Dr.Sangüeza, dear Omar

We are submitting the enclosed manuscript "CD8+ small to medium-sized lymphoproliferations of the skin in extrafacial sites - clinicopathological features and concepts on their classification" as an Original article to the Journal. We report the clinicopathological features of three cases of CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites. This is the first case series of extrafacial CD8+ lymphoproliferations. In addition, we discuss the relationsship to other small/medium-sized lymphoproliferations.

We appreciate your efforts in the evaluation of our manuscript. Thank you in advance.

Yours sincerely,

Werner Kempf

CD8+ small to medium-sized lymphoproliferations of the skin in extrafacial sites - clinicopathological features and concepts on their classification

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Running title: Extrafacial CD8+ lymphoid proliferation

Key words: CD8, extrafacial, lymphoproliferative, small to medium-sized, lymphoma, pseudolymphoma

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Abstract

Three cases of CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites are described. Clinically, the patients presented with papulo-nodular or plaque-like lesions without preceding patches. Histopathologically, non-epidermotropic nodular or diffuse infiltrates were composed of small to medium sized pleomorphic lymphocytes which expressed CD8 (more than 80% of the cells) and granzyme B (60-70% of the cells), but were negative for CD4, CD30 and CD56. There was no association with Epstein-Barr virus. A clonal T-cell population was detected in one patient. Staging examinations did not reveal extracutaneous involvement. The two patients with solitary lesions underwent complete remission after radiation therapy, whereas one patient developed multifocal lesions and several recurrences. The CD8+ small to medium-sized lymphoproliferations of the skin at extrafacial sites may belong to a spectrum of a phenotypically and prognostically heterogeneous cutaneous small to medium-sized lymphoid proliferations which are characterized by an indolent course in most patients.

Key words cutaneous small to medium-sized pleomorphic T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, cutaneous peripheral T-cell lymphoma not otherwise specified, cytotoxic lymphoma, indolent CD8-positive lymphoid proliferation of the ear, pseudolymphoma

Introduction

In the recent literature, there have been several reports of unusual CD8+ lymphoid proliferations of the skin which posed diagnostic problems, especially with regard to their classification according to the currently used schemes, and particularly the WHO/EORTC classification of cutaneous lymphomas. (1), (2), (3), (4) Those cases clearly differed from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (CTCL), as well as from other lymphoma type with CD8 expression such as subcutaneous panniculitis-like T-cell lymphoma, and lymphomas with occasional expression of CD8 such as mycosis fungoides, cutaneous gamma/delta T-cell lymphoma, and extranodal NK/T-cell lymphoma, nasal type (5), (6), (7), (8) Cases in which the lesions were located on the face, often involving the ear have been referred to as "indolent CD8-positive lymphoid proliferation of the ear and face", respectively are characterized by nodular infiltrates of small to medium-sized CD8-positive lymphocytes. So far only 2 patients with a nodular infiltrate of CD8+ small to medium-sized lymphocytes has been reported in acral, i.e. extrafacial location. (9), (10) A common clinical feature of the reported cases of CD8+ small to medium-sized lymphoid infiltrates was an indolent course, which is in contrast to a rare subset of peripheral CTCL, not otherwise specified (NOS) with a cytotoxic phenotype which usually follows an aggressive course. (11) Some authors felt that the infiltrates of CD8+ small to medium-sized lymphocytes cases are morphologically related to primary cutaneous small to medium-sized pleomorphic T-cell lymphoma (SMPTL) except for the fact that the small to medium-sized lymphocytes in SMPTL express CD4 (1), (2), (3), (4) Here we present the clinicopathological features of three cases of extrafacial small to medium sized CD8+ lymphoproliferations of the skin and discuss their possible categorization.

Material and Methods

A total of 6 biopsies from 3 patients were available for a histopathological review. Biopsy specimens were fixed in 10% buffered formalin and sections were routinely processed and embedded in paraffin. Serial 4 micrometer-thick sections were cut for hematoxylin and eosin stains as well as immunohistochemical stains. The antibodies used for immunohistochemistry included: CD2 (1:50, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD3 (1:75, Dako, Glostrup, Denmark), CD4 (1:2, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD7 (1:25, Dako, Glostrup, Denmark), CD8 (1:400, Dako, Glostrup, Denmark), CD20 (1:600, Dako, Glostrup, Denmark), CD30 (1:75; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD56 (RTU, Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), and TIA-1 (1:50, Immunotech Marseille, France), as well as granzyme B (1:50; Dako, Glostrup, Denmark) and perforin (1:20; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), beta F1 (1:50, Thermo Scientific, Germany). Immunostaining was performed according to standard protocols using alkaline phosphatase-anti-alkaline phosphatase method, avidin-biotin complex or streptavidin-biotin complex labeled with peroxidase or alkaline

phosphatase. Appropriate positive and negative controls were applied. The antibody panel used differed in individual cases depending on the availability of the tissue/antibodies.

In all cases, molecular T-cell receptor (TCR) rearrangement studies were performed using a multiplex polymerase chain reaction (PCR) as described elsewhere. (12) Appropriate positive and negative controls were included in all analyses. Also, in situ hybridization for EBV was performed.

Results

Clinical data

Case 1. A 48-year old man presented in June 2007 with an erythematous nodule (diameter 1cm) on the right buttock. The patient's history was significant for Bruton's X-linked agammaglobulinemia that had been treated with immunoglobulin substitution for the previous 21 years. The lesion was excised. Three years later (April 2010) the patient developed infiltrated slightly brownish plaques on the dorsal aspects of the left foot and toes (Figure 1A). Following histopathological diagnosis with a suspicion for cytotoxic lymphoma the patient was clinically investigated to exclude extracutaneous disease (including PET-CT, peripheral blood investigation), but no extracutaneous involvement was found. In May 2010 the lesions were treated with radiation therapy (total dose 32 Gy using 100kV) with complete regression. In March 2011 a relapse with a plaques on the left foot was observed (Figure 1B) which was treated by radiation therapy (total dose 52 Gy using 40kV; March to June 2011) which again resulted in complete regression of the lesions. Three months later, the patient developed the second recurrence of small livid papules on the left foot adjacent to the radiation site and in addition 3 small papulo-nodular lesions (diameter up to 8mm) in the right retroauricular area. The staging examinations (PET/CT, peripheral blood investigations) were repeated and remained negative. In parallel to the superficial X-ray irradiation for the retroauricular lesions, treatment with low-dose methotrexate (15mg/week) was started in November 2011 and resulted in complete remission until last follow-up in January 2012. Several biopsies of the lesions on the right buttock, the lesions on the feet and the retroauricular papulo-nodular lesions were histologically examined.

Case 2. An 87-year-old woman presented with a solitary, red infiltrated non-scaling plaque (diameter 5 cm) on the right lower leg (Figure 2). Her medical history was unremarkable for skin diseases or neoplastic diseases. The clinical examination did not reveal enlarged lymph nodes. The lesion was treated by radiation therapy (total dose 50 Gy). No recurrence was observed during follow-up of 2 years.

Case 3. A 52-year-old man presented with a 1.3x0.8 cm solitary nodule on the right shoulder. The lesion was completely excised. The staging examinations did not reveal any extracutaneous involvement. One year later, on a regular check-up no evidence of cutaneous and extracutaneous disease. Blood examinations revealed a mild lymphocytosis, but no atypical lymphocytes. All findings were normal at the last follow up 26 months after diagnosis.

Histopathologic, immunophenotypic and molecular findings

Common to all cases was a dense nodular to diffuse dermal infiltrate composed mainly of small and medium sized lymphocytes were found which were separated from the overlying epidermis by a variably thick Grenz zone (Figures 1C, 3A and 3B). The epidermis was either normal or focally atrophic with a loss of the undulated pattern. Specifically, no epidermotropism was observed in any of the biopsies of all three patients (Figure 3B). In all biopsies, the small to medium-sized lymphocytes showed chromatin dense nuclei with mild to moderate nuclear pleomorphism with cleaved nuclei (Figures 1D and 3C). A few eosinophilic granulocytes were admixed. In patient 1, several biopsies showed a granulomatous component with numerous histiocytes occasionally forming small epithelioid granulomas in addition to the lymphocytic infiltrate (Figure 1E). In addition, the lymphocytic infiltrates were centered on a slightly hyperplastic hair follicle but there was no folliculotropism in one of the biopsies of the acral lesions in patient 1 (Figure 1C).

Immunohistochemically, the small to medium-sized lymphocytes were strongly positive for CD8, with about 80-90% of the cell population staining for this marker in each specimen (Figures 1F, 3D and 3E) (Table 1). A minority of the small lymphocytes (10-30% of the cells) expressed CD4 (Figures 1G and 3F). The cells expressed other T-cell markers (CD2, CD3 [except for patient 3], CD5 and CD7) and were positive for betaF1 (Figure 3G). The CD8+ lymphocytes were negative for TIA-1, but granzyme B was expressed by 60-70% of the small to medium-sized lymphocytes in the biopsies of patient 1 and 2. In the biopsies of all patients, the lymphocytes were consistently negative for CD30 and CD56. There was an admixture of scattered medium-sized B-cells in the biopsy of patient 3. Less than 10 percent of the small to medium-sized CD8+ lymphocytes displayed proliferative activity in the Ki67/MIB-1 staining (Figure 1H). In the two patients (patients 1 and 3), from whom multiple biopsied were studied, the immunoprofile of the lymphoid cells was identical in each specimen. In situ hybridization performed in biopsies of patient 1 and 2 were negative. Due to lack of remaining tissue, this examination could not be performed in patient 3.

Molecular biological T-cell clonality analyses revealed a clonal T-cell population in the biopsy of patient 2, whereas the infiltrates in the patient 1 and patient 3 were polyclonal.

Discussion

The common clinicopathological features to all our cases are papulo-nodular or plaque-like lesions without preceding patches and histologically nodular proliferations of small to medium sized CD8+ lymphocytes lacking epidermotropism. In the context of cutaneous lymphoid infiltrates, cases showing a cytotoxic phenotype should always alert the pathologist to a possibility of an aggressive cutaneous lymphoma but the lesions were report on are clearly different, both clinically and histopathologically, from aggressive cytotoxic lymphomas such as

primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma and other aggressive lymphoma type in which CD8 expression is commonly or occasionally observed such as subcutaneous panniculitis-like T-cell lymphoma, cutaneous gamma/delta T-cell lymphoma, and extranodal NK/T-cell lymphoma, nasal type. (13), (14), (15) CD8 phenotype has rarely been observed in less aggressive or rather indolent CTCL including mycosis fungoides, pagetoid reticulosis and CD30+ anaplastic large cell lymphoma. (16), (17), (18), (19) A cytotoxic infiltrate has recently been found in peculiar form of lupus erythematosus which showed an overlap of clinicopathological features with subcutaneous panniculitis-like T-cell lymphoma with overlapping clinicopathological features of lupus erythematosus. (20) All of the above diagnoses were clearly excluded in our patients. In particular, the lack of epidermotropism in all biopsies and the absence of preceding patches argue against CD8+ variant of MF as well as primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. Cutaneous gamma/delta lymphoma is excluded by the presence of beta F1 expression. The indolent clinical course and the lack of association with EBV exclude extranodal NK/T-cell lymphoma.

Histopathologically, our cases are very similar to those reported as indolent CD8+ lymphoid proliferation of the ear (or face) but in all of our patients the lesions were located in extrafacial sites. So far, 5 patients (including our 3 patients) with CD8+ small/medium-sized lymphoid infiltrates at extrafacial sites have been reported (9), (10) Their clinicopathologic features are summarized in Table 1. From the clinical aspect, the histological findings as well as the phenotype of the small to medium-sized lymphocytes, our cases are rare very similar or even identical to the patient reported by Khamaysi et al which was interpreted by the authors as CD8+ small to medium sized pleomorphic CTCL. (10) Classification of the CD8+ lymphoid infiltrates in our cases is challenging. Although the term cutaneous peripheral T-cell lymphoma, NOS (PTL, NOS) can be applied to cases which do not fit into any of the well-defined forms of CTCL and CD8 phenotype has indeed been observed in peripheral T-cell lymphoma, NOS, including cases with small to medium sized cytomorphology, such tumors usually run an aggressive clinical course. In a large study, cytotoxic phenotype has been found in about 15% of peripheral T-cell lymphoma, NOS, and a median survival of the affected patients was 28 months. (11) Clinically, our cases show a similar biological behavior as seen in CD4+ SMPTL which manifests in the vast majority of the patients with solitary or grouped plaques or nodules and run an indolent course with an excellent prognosis (11), (21) Therefore our cases could be regarded as a phenotypic CD8+ lymphoproliferative analogue to the CD4+ SMPTL (Figure 4).

In regard to the indolent course and the overlapping histological features, some authors indicated that CD4+ SMPTL cannot be distinguished with certainty form nodular pseudo-T-cell lymphoma and therefore proposed the term "cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance (21), (22). In fact, some cases of pseudolymphoma composed of small and occasional medium sized cells may be overdiagnosed at present as small to medium sized pleomorphic T-cell lymphoma. (21), (23) Moreover, a CD8 phenotype has been reported in

rare cutaneous pseudolymphomas in HIV positive patients and other conditions characterized by lymphoid infiltrates, including lymphoid infiltration of Jessner-Kanof and palpable acriform migratory erythema (24), (25), (26) However, these lesions manifest a less prominent infiltrate composed almost exclusively of small cells. The possibility that the infiltrate in our patient 3 represents a form of pseudolymphoma (reactive lymphoid hyperplasia) cannot be totally refuted, although no association with drug intake was reported by the patient. In addition, the lack of CD3 expression by the small to medium-sized tumor cells argues against pseudolymphoma.

Patients with SMPTL appear to have a favorable prognosis independent of their CD4 or CD8 - positive phenotype, especially those with a solitary lesion (10), (27), (9), (23) Nevertheless, the relapsing course and the multifocal occurrence of tumoral lesions in patient 1 may indicate that the extrafacial CD8+ lymphoproliferations may in fact represent a prognostically heterogenous group as it has also been reported in CD4+ SMPTL. In the latter entity, cases with multiple rapidly growing tumors and a high proliferation rate may run a more aggressive course. (28) Thus a patient with multiple lesions should be followed more intensively and may require more intense treatment.

An interesting feature observed in one case (Case 1) was the conspicuous granulomatous infiltration in the first biopsy. In the context of cutaneous lymphomas, granulomatous features are typically present in granulomatous slack skin and granulomatous mycosis fungoides and are rare in other lymphoma types. (29), (30), (31), (32) They have also been described in so-called pseudolymphomatous folliculitis, the term used to describe a distinctive pattern seen in both lymphomas and pseudolymphomas. (33), (34) Along this line, some cases of "pseudolymphomatous folliculitis" and small to medium-sized pleomorphic CTCL show a great clinicopathological overlap. (34), (35), (36) Whether in our patient the granulomatous (and lymphomatous) infiltrate who suffered from Bruton's X-linked agammaglobulinemia may be related to immunoglobulin substitution or remains speculative. Similar histopathological findings have recently been reported in a Japanese patient afflicted X-linked agammaglobulinemia, including a heavy small to medium sized non-epidermotropic lymphoid infiltrate with cytotoxic CD8+ phenotype and a great admixture of histiocytes. (37) The tumor was classified as peripheral CTCL, NOS and the patient clinically presented with multiple papules, macules and patches on the face and trunk. (37)

In conclusion, we report a series of CD8+ small to medium-sized cell lymphoproliferations of the skin with an indolent behavior similar to those reported for CD8+ lymphoid proliferation on the ear and face, but all occurring in extrafacial sites. Further observations are needed collect a larger number of such cases in order to get insight into the biologic nature of the lesion (lymphoma or reactive process) and to find out whether they represent a prognostically heterogeneous group of lesions. If such lymphoproliferations would be classified as lymphoma, then according to the currently used schemes (WHO classification, 2008, 4th edition) they would

conform to the concept of cutaneous PTL, NOS and can perhaps be regarded as the CD8+ analogue of CD4+ SMPTL within a larger spectrum of nodular infiltrates of small to medium-sized pleomorphic lymphocytes (Figure 4). A growing body of evidence suggests that what is nowadays called small to medium sized pleomorphic CTCL may in fact represent a phenotypically and prognostically heterogeneous group of lymphoproliferations. (28)

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Figures

Figure 1: Patient 1 - Clinicopathologic findings

Fig. 1A: Scaly brownish plaque on the left foot at initial presentation.
Fig. 1B: Relapse with erythematous papules adjacent to the site of previous radiation therapy.
Fig. 1C: Superficial and deep nodular and confluent infiltrates. H&E, original magnification X20
Fig. 1D: Small to medium-sized pleomorphic lymphocytes, H&E, original magnification X400
Fig. 1E: Granulomatous component with sarcoid-like granulomas and numerous small to medium-sized lymphocytes with nuclear atypia. H&E, original magnification X200,
Fig 1F: Expression of CD8 (red) by more than 80% of the small to medium-sized lymphocytes. Immunohistochemistry, original magnification X200.
Fig 1G: Only small lymphocytes accounting for less than 20% of the infiltrate express CD4. (red). Immunohistochemistry, original magnification X200.
Fig 1H: Proliferative activity of less than 10% of small to medium-sized pleomorphic lymphocytes.

Figure 2: Patient 2 - Erythematous plaque on the right lower leg

Figure 3: Patient 3 - Histological and phenotypic findings

Fig 3A: Superficial and deep nodular infiltrates. H&E, original magnification X20
Fig. 3B: Lymphocytic infiltrates separated from the overlying epidermis by an infiltrate-free Grenz zone. H&E, original magnification X200
Fig. 3C: Small to medium-sized pleomorphic lymphocytes, H&E, original magnification X400
Fig. 3D: Expression of CD8 (red) by nearly all lymphocytes. Immunohistochemistry, original magnification X100.
Fig. 3E: Expression of CD8 (red) by more than 80% of the small to medium-sized pleomorphic lymphocytes. Immunohistochemistry, original magnification X200.
Fig. 3F: Expression of CD4 (red) by less than 10% of the small to medium-sized pleomorphic lymphocytes. Immunohistochemistry, original magnification X200.
Fig 3G: Less than 25% of the small to medium-sized pleomorphic lymphocytes express CD3 (red). Immunohistochemistry, original magnification X200.

Figure 4: Concept on the relationship between primary cutaneous small to medium-sized T-cell lymphoma with CD4+ or CD8+ expression, cutaneous CD8+ lymphoid proliferation of the ear / face and nodular pseudo-T-cell-lymphoma.

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Table 1. The main clinicopathological features of cutaneous CD8+ small to medium sized lymphoid proliferations in extrafacial sites

Case	Sex/Age	Location	Clinical features	Treatment Follow-up	Histology	IHC	TCR
Case 1	M/48	Buttock (2007) Lower leg (2010)	Multiple infiltrative papules and plaques	Radiation therapy, Methotrexat (low-dose) Alive with disease (FU: 48 months)	Nodular infiltrate Small to medium sized cells; no epidermotropism Granulomatous reaction in one specimen	CD2+, CD3+, CD4 (30%), CD5+,CD8 (80%), CD30-, CD56-, granzyme (70%), perforin -TIA1 (890%)	Negative
Case 2	F/87	Lower leg	Red infiltrated plaque	Radiation therapy Complete remission (FU: 24 months)	Diffuse infiltrate Small to medium sized cells; no epidermotropism	CD2+, CD3+, CD4(30%), CD5+, CD7+ CD8 (80%), CD30-, CD56-, granzyme B (60%), perforin -, TIA1 (70%)-	Positive
Case 3	M/54	Shoulder	1.3x0.8 cm solitary nodule	Surgical excision Complete remission (FU: 28 months)	Nodular infiltrate Small to medium sized cells; no epidermotropism	CD3-,CD4 10%), CD5+,CD8 (90%), CD30-, CD56-	Negative
Case reported by Khamaysi et al 2006	F/55	Right foot	Erythematous nodule (diameter 2cm)	Radiation therapy and surgical excision No FU available	Lichenoid infiltrate Small to medium sized cells; no epidermotropism	CD3+, CD8+ CD4- CD20. CD30-, CD56-	Positive
Case reported by Friedmann et al. 1995	F/57	Widespread lesions	Tumors and nodules	Mechlorethamine, radiation therapy, Psoralen-UVA (PUVA), Interferon-alpha (FU: no evidence of disease at 86 months)	Small to medium sized cells; no epidermotropism	CD3+ ,CD8+ (50-75%) CD4 (<25%) CD5+, CD7- CD30- CD20 (<25%)	Positive

FU: Follow-up

ND: not done

NR: not reported